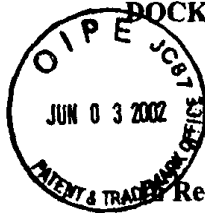


1645 #5  
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PATENT



DOCKET NO.: ISIS-5028

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re Application of:

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JUN 06 2002

Philip D. Cook et al.

Serial No.: 10/080,979

Group Art Unit: 1645

TECH CENTER 1600/2900

Filing Date: February 22, 2002

Examiner: Not yet assigned

For: **METHOD OF USING MODIFIED OLIGONUCLEOTIDES FOR HEPATIC  
DELIVERY**

DATE OF DEPOSIT: May 22, 2002

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Wendy A. Choi  
TYPED NAME: Wendy A. Choi  
REGISTRATION NO.: 36,697

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

### INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

- ☒ In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first office action after the filing of request for continued examination under §1.114, no additional fee is required.

- ☐ In accordance with §1.129(a), this Information Disclosure Statement is being filed in connection with ☐the first or ☐second After Final Submission, therefore:
- ☐ Certification in Accordance with §1.97(e) is attached; or
- ☐ The fee of **\$180.00** as set forth in §1.17(p) is attached.
- ☐ In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311, or before an action that otherwise closes prosecution in the application, therefore:
- ☐ Certification in Accordance with §1.97(e) is attached; or
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- ☐ In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with §1.97(e); and the submission fee of **\$180.00** as set forth in §1.17(p).
- ☒ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.
- ☐ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:
- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☐ In accordance with §1.98(d), copies of the following references listed on the attached Form PTO-1449 are not enclosed herewith because they were

previously cited by or submitted to the U.S. Patent and Trademark Office in patent application(s) for which a claim for priority under 35 U.S.C. §120 have been made in the instant application:

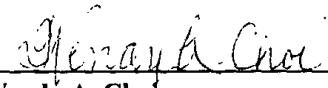
- ☐ Copies of references [list as appropriate] listed on the attached Form PTO-1449 were previously cited by or submitted to the Patent and Trademark Office in prior application Serial No. , filed .
- ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

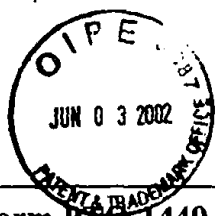
This form is submitted in duplicate.

There are no listed references which are not in the English language.

Date: May 22, 2002

  
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<b>Form PTO-1449 Modified</b>		Docket No. <b>ISIS-5028</b>	Serial No. <b>10/080,979</b>
List of Patent and Publications Cited by Applicant (Use several sheets if necessary)		Applicant <b>Philip D. Cook et al.</b>	
		JUN 06 2002	
U.S. Department of Commerce Patent and Trademark Office		Filing Date <b>February 22, 2002</b>	Group <b>1645</b> TECH CENTER 1600/291
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
AA	Bijsterbosch et al., "In vivo fate of phosphorothioate antisense oligodeoxynucleotides: predominant uptake by scavenger receptors on endothelial liver cells," <i>Nucl. Acids Res.</i> , 1997, 25(16):3290-3296		
AB	Bijsterbosch et al., "Modulation of plasma protein binding and in vivo liver cell uptake of phosphorothioate oligodeoxynucleotides by cholesterol conjugation," <i>Nucl. Acids Res.</i> , 2000, 28(14):2717-2725		
AC	Graham, M.J. et al., "Tritium Labeling of Antisense Oligonucleotides by Exchange with Tritiated Water", <i>Nucleic Acids Res.</i> 1993, 21(16), 3737-3743.		
AD	Letsinger, R.L., et al., "Cholesteryl-Conjugated Oligonucleotides: Synthesis, Properties, and Activity as Inhibitors of Replication of Human Immunodeficiency Virus in Cell Culture", <i>Proc. Natl. Acad. Sci. USA</i> 1989, 86, 6553-6556.		
AE	Manoharan, et al., "Chemical Modifications to Improve Uptake and Bioavailability of Antisense Oligonucleotides" <i>Database Embase Elsevier Science Publishers</i> 1992 660, 306 (abstract)		
AF	Manoharan M. et al., "Cholic Acid-Oligonucleotide Conjugates for Antisense Applications", <i>Bioorganic Med. Chem. Letts.</i> , 1994, 4, 1053-1060		
AG	Manoharan M. et al., "Oligonucleotide Conjugates: Alteration of the Pharmacokinetic Properties of Antisense-Agents", <i>Nucleosides and Nucleotides</i> , 1995, 14, 969-973		
AH	Nagelkerke, J.F. et al., "In Vivo and in Vitro uptake and degradation of Acetylated Low Density Lipoprotein by Rat Liver Endothelial, Kupffer, and Parenchymal Cells", <i>J. Biol. Chem.</i> , 1983, 263:12221-12227		
AI	Rump, E.T. et al., "Preparation of Conjugates of Oligodeoxynucleotides and Lipid Structures and Their Interaction with Low-Density Lipoprotein", <i>Bioconjugate. Chem.</i> , 1998, 9341-349		
AJ	Wong, J. et al., "Role of Icam-I in chronic hepatic allograft rejection", <i>Hepatology</i> , 1997, 26:165A		
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>	